



4160-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2013-P-0241]

Determination That CYTOXAN (Cyclophosphamide) for Injection Was Not Withdrawn From Sale for Reasons of Safety or Effectiveness

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) has determined that CYTOXAN (cyclophosphamide) for Injection (lyophilized formulations), 100 milligrams (mg)/vial, 200 mg/vial, 500 mg/vial, 1 gram (g)/vial, and 2 g/vial, and CYTOXAN (cyclophosphamide) for Injection (non-lyophilized formulations), 100 mg/vial and 200 mg/vial, were not withdrawn from sale for reasons of safety or effectiveness. This determination will allow FDA to approve abbreviated new drug applications (ANDAs) for these products, if all other legal and regulatory requirements are met.

FOR FURTHER INFORMATION CONTACT: Christine Kirk, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, rm. 6280, Silver Spring, MD 20993-0002, 301-796-2465.

SUPPLEMENTARY INFORMATION: In 1984, Congress enacted the Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) (the 1984 amendments), which authorized the approval of duplicate versions of drug products under an ANDA procedure.

ANDA applicants must, with certain exceptions, show that the drug for which they are seeking approval contains the same active ingredient in the same strength and dosage form as the "listed

drug," which is a version of the drug that was previously approved. ANDA applicants do not have to repeat the extensive clinical testing otherwise necessary to gain approval of a new drug application (NDA).

The 1984 amendments include what is now section 505(j)(7) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(j)(7)), which requires FDA to publish a list of all approved drugs. FDA publishes this list as part of the "Approved Drug Products With Therapeutic Equivalence Evaluations," which is known generally as the "Orange Book." Under FDA regulations, drugs are removed from the list if the Agency withdraws or suspends approval of the drug's NDA or ANDA for reasons of safety or effectiveness or if FDA determines that the listed drug was withdrawn from sale for reasons of safety or effectiveness (21 CFR 314.162).

A person may petition the Agency to determine, or the Agency may determine on its own initiative, whether a listed drug was withdrawn from sale for reasons of safety or effectiveness. This determination may be made at any time after the drug has been withdrawn from sale, but must be made prior to approving an ANDA that refers to the listed drug (§ 314.161 (21 CFR 314.161)). FDA may not approve an ANDA that does not refer to a listed drug.

CYTOXAN (cyclophosphamide) for Injection (lyophilized formulations), 100 mg/vial, 200 mg/vial, 500 mg/vial, 1 g/vial, and 2 g/vial, and CYTOXAN (cyclophosphamide) for Injection, 100 mg/vial and 200 mg/vial, are the subject of NDA 012142, held by Baxter Healthcare, and initially approved on November 16, 1959. CYTOXAN for Injection is an alkylating drug product indicated for treatment of malignant lymphomas, Hodgkin's disease, lymphocytic lymphoma, mixed-cell type lymphoma, histiocytic lymphoma, Burkitt's lymphoma, multiple myeloma, leukemias, mycosis fungoides, neuroblastoma, adenocarcinoma of ovary, retinoblastoma, breast carcinoma, and minimal change nephrotic syndrome in pediatric patients.

CYTOXAN (cyclophosphamide) for Injection (lyophilized formulations), 100 mg/vial, 200 mg/vial, 500 mg/vial, 1 g/vial, and 2 g/vial, and CYTOXAN (cyclophosphamide) for Injection, 100 mg/vial and 200 mg/vial, are currently listed in the "Discontinued Drug Product List" section of the Orange Book.

Foley & Lardner LLP submitted a citizen petition dated February 26, 2013 (Docket No. FDA-2013-P-0241), under 21 CFR 10.30, requesting that the Agency determine whether CYTOXAN (cyclophosphamide) for Injection (lyophilized formulations), 100 mg/vial, 200 mg/vial, 500 mg/vial, 1 g/vial, and 2 g/vial, were voluntarily withdrawn or withheld from sale for reasons of safety or effectiveness. Although the citizen petition did not address the non-lyophilized 100 mg/vial and 200 mg/vial formulations, those strengths have also been discontinued. On our own initiative, we have also determined whether those strengths were withdrawn for safety or effectiveness reasons.

After considering the citizen petition and reviewing Agency records and based on the information we have at this time, FDA has determined under § 314.161 that CYTOXAN (cyclophosphamide) for Injection (lyophilized formulations), 100mg/vial, 200mg/vial, 500 mg/vial, 1 g/vial, and 2 g/vial, and CYTOXAN (cyclophosphamide) for Injection, 100 mg/vial and 200 mg/vial, were not withdrawn for reasons of safety or effectiveness. The petitioner has identified no data or other information suggesting that CYTOXAN (cyclophosphamide) for Injection (lyophilized formulations), 100 mg/vial, 200 mg/vial, 500 mg/vial, 1 g/vial, and 2 g/vial, or CYTOXAN (cyclophosphamide) for Injection, 100 mg/vial and 200 mg/vial, were withdrawn for reasons of safety or effectiveness. We have carefully reviewed our files for records concerning the withdrawal of CYTOXAN (cyclophosphamide) for Injection (lyophilized formulations), 100 mg/vial, 200 mg/vial, 500 mg/vial, 1 g/vial, and

2 g/vial, and CYTOXAN (cyclophosphamide) for Injection, 100 mg/vial and 200 mg/vial, from sale. We have also independently evaluated relevant literature and data for possible postmarketing adverse events. We have found no information that would indicate that these products were withdrawn from sale for reasons of safety or effectiveness.

Accordingly, the Agency will continue to list CYTOXAN (cyclophosphamide) for Injection (lyophilized formulations), 100 mg/vial, 200 mg/vial, 500 mg/vial, 1 g/vial, and 2 g/vial, and CYTOXAN (cyclophosphamide) for Injection, 100 mg/vial and 200 mg/vial, in the "Discontinued Drug Product List" section of the Orange Book. The "Discontinued Drug Product List" delineates, among other items, drug products that have been discontinued from marketing for reasons other than safety or effectiveness. ANDAs that refer to CYTOXAN (cyclophosphamide) for Injection (lyophilized formulations), 100 mg/vial, 200 mg/vial, 500 mg/vial, 1 g/vial, and 2 g/vial, or CYTOXAN (cyclophosphamide) for Injection, 100 mg/vial and 200 mg/vial, may be approved by the Agency as long as they meet all other legal and regulatory requirements for the approval of ANDAs. If FDA determines that labeling for these drug products should be revised to meet current standards, the Agency will advise ANDA applicants to submit such labeling.

Dated: July 30, 2013.

Leslie Kux,

Assistant Commissioner for Policy.